REMARKS

In a final Office Action mailed on January 11, 2006, claims 1-6, 8-21, 23-25 and 43-45 were rejected. Claims 27-39 have been withdrawn as being drawn to non-elected inventions. Thus, claims 1-6, 8-21, 23-25, and 43-45 are pending. Applicant respectfully requests reconsideration of these pending claims.

Rejection under 35 U.S.C. § 103

Claims 1-3, 6, 8, 15-21, and 24 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Krieg *et al.* (WO 98/18810, "Krieg") in view of Schwartz *et al.* (WO 98/55495, "Schwartz"). In particular, the Office Action alleges:

> In view of the combined teachings of Krieg *et al* and Schwartz *et al* it would have been obvious to a person of ordinary skill in the art to prepare a composition that comprises a CG oligonucleotide and a Neisseria antigen and optionally another adjuvant. The prior art teaches that the Neisseria antigen can be *Neisseria meningitidis*, or *Neisseria gonorrhoeae* and an adjuvant composition comprising an oligonucleotide comprising at least one CG motif. Krieg *et al* teaches the claimed oligonucleotide as set forth in SEQ ID NO:1 and teaches that it is a strong immune activating sequence and is a superb adjuvant. Both references teach the use of multiple adjuvants in the compositions. Schwartz et al teaches that the specifically claimed additional adjuvants can be used in the compositions to enhance the immunomodulatory activity. (Final Office Action, pages 5-6.)

In addition, claims 1-6, 8-21, and 43-45 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Agrawal *et al.* (WO 98/49288, "Agrawal") in view of Fraser *et al.* (WO 99/57280, "Fraser"). In particular, the Office Action alleges:

> In view of the combined teachings of Agrawal et al and Fraser et al it would have been obvious to a person of ordinary skill in the art to prepare a composition comprising a Neisseria antigen (*Neisseria meningitidis* serogroup B and *Neisseria gonorrhoeae*) and an adjuvant composition comprising an oligonucleotide comprising at least one CG motif. Agrawal et al teaches the claimed oligonucleotide as set forth in SEQ ID NO:1 and teaches that it has adjuvant or immunostimulating properties as well as the fact that Agrawal et al.

> teaches treating bacterial infections and diseases. Both references teach the use of multiple adjuvants in the compositions. Fraser et al teaches the specific antigen of Neisseria claimed by Applicants set forth in SEQ ID NO:31 and teaches that all of these antigens can be used in vaccine, pharmaceutical and therapeutic compositions. (Final Office Action, page 8.)

Applicant respectfully traverses the rejections under 35 U.S.C. § 103 and their supporting remarks on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

The claims are directed to immunogenic compositions comprising a Neisseria meningitidis serogroup B antigen, a CpG oligonucleotide, and an emulsion comprising submicron oil droplets and an emulsifying agent. None of the cited references teach or suggest the claimed immunogenic compositions.

1. *Fraser is Unavailable as Prior Art*

The Examiner has asserted that the pending claims are not entitled to claim priority to the provisional application as it lacked the sequence in the present claims. Applicants respectfully disagree. Page 26, lines 10-18 of the priority provisional application disclose the presently claimed SEQ ID NO: 31 and even includes the proper SEQ ID NO, which is not required for provisional applications. Thus, the present claims are entitled to claim priority as of the filing of the provisional application on February 26, 1999. Fraser *et al.* was filed prior to November 29, 2000, so it is only entitled to a 102(e) date (i) as of entry into the national phase in the U.S. and completion of 35 U.S.C. 371(c)(1), (2), and (4) or (ii) the filing date of the later-filed U.S. Application which claims the benefit of the application. (See MPEP2136.03(I)(C)) Alternatively, the publication date of November 11, 1999 is after the present application's claim of priority. Therefore, unless the Examiner demonstrates that there is a U.S. Application claiming the benefit of Fraser et al. filed

before February 26, 1999 or a nation stage filing from Fraser et al. that satisfied the requirements of 35 U.S.C. 371(c)(1), (2), and (4) before February 26, 1999, Applicants respectfully request that the Examiner withdraw the rejection over Agrawal *et al.* in view of Fraser *et al.*

2. *Missing element*

The Examiner has acknowledged that neither § 103 rejection supplies the limitation wherein "at least 80% of said oil droplets are less than 1 micron in diameter." The Examiner asserts that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the diameter size and ratios, since it has been held that discovering an optimum value of a ***result effective variable*** involves only routine skill in the art." However, the Examiner has not established that droplet size was a known result effective variable prior to the filing of the present application. If one of skill in the art did not know that a variable should be manipulated to optimize a result, then it could not be obvious to optimize the variable. The applicants respectfully assert that both of the obviousness rejections fail to teach or suggest this limitation and therefor the Examiner has not established a *prima facie* case of obviousness.

3. *No motivation to combine.*

A. Krieg in view of Schwartz

Krieg was cited for teaching that CpG oligonucleotides can be used to treat infectious bacteria, including *Neisseria gonorrhoeae* and *Neisseria meningitidis*. Schwartz was cited for disclosing compositions comprising CpG oligonucleotides in combination with antigens and other adjuvants, including oil-in-water emulsions. However, neither Krieg nor Schwartz describe or suggest an immunogenic composition comprising a *Neisseria* antigen, as claimed. Krieg's only mention of *Neisseria* is in a laundry list of infectious bacteria (page 17). In fact, Krieg fails to describe any immunogenic compositions comprising *Neisseria* antigens. Krieg only describes compositions of nucleic acids containing a CpG motif. Schwartz fails to even mention *Neisseria*. Therefore, no combination of these references discloses or suggests all the limitations of the claims.

B. Agrawal in view of Fraser

Agrawal was cited for teaching compositions comprising a Neisseria antigen and an adjuvant composition comprising a CpG oligonucleotide. Fraser was cited for teaching antigens of *Neisseria meningitidis* and *Neisseria gonorrhoeae* including an antigen comprising the amino acid sequence of SEQ ID NO:31 of the instant application, and adjuvants comprising submicron oil-in-water emulsions that can be used in immunogenic compositions. However, Agrawal suggests the use of the CpG oligonucleotide with antigens from a laundry list of organisms one of which is *Neisseria spp.* Fraser suggests a broad range of adjuvants, which notably does not mention CpG oligonucleotides. Neither reference teaches or suggests the desirability of the particular combination of adjuvants and antigens as is presently claims.

C. Conclusion

In the absence of some teaching or suggestion in the cited references concerning the immunogenic compositions described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims cannot be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness even when all claimed elements are individually present in the references. See, *e.g.*, *In re Kotzab* 217 F.3d 1365, (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would

have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, *e.g.*, *In re Rouffet*. 47 USPQ2d 1453 (Fed. Cir. 1998), noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the invention, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such citation. Instead, the Examiner has merely asserted that it would have been obvious to combine compositions comprising a CpG oligonucleotide and a *Neisseria* antigen with an additional adjuvant. However, none of the cited references specifically teach or suggest the additional adjuvant comprising submicron oil droplets and an emulsifying agent as claimed. In particular, none of the references teach the ratio of oil to emulsifying agent, or the size of oil droplets in the emulsion. Nevertheless, Applicants have added the additional limitation that the antigen in the immunogenic compositions be a *Neisseria meningitidis* serogroup B antigen.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Here, the Office cites prior art disclosure of two different 2-way combinations of references directed at immunogenic compositions as motivation to "pick and chose" a non overlapping 3-way combination of agents from the respective pairs of references, without citing to the motivation for the particular combination. Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

4. *Improper 'Obvious to Try'.*

A. Krieg in view of Schwartz

Review of Schwartz *et al.* for their suggested costimulatory molecules to combine with Schwartz *et al.* ISS molecule reveals a sizable list that includes IL-1, IL-2, IL-4, IL-5, IL-6, IL-12, IFN-γ, TNF-α, "and the like" and oil-in-water emulsions, water-in oil emulsions, alum, liposomes, polystyrene microparticles, starch microparticles, polyphosphazene microparticles, polylactide/polyglycoside microparticles, squalene mixtures, muramyl peopdies, saponin derivatives, mycobacterium cell wall preparations, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, ISCOMs, and Freund's adjuvant (complete and incomplete) (see page 12 and pages 15-19, as cited by the Examiner). Thus, review of only the pages cited by the Examiner produces 29 different costimulatory molecules mentioned by Schwartz *et al.*, a number of which are themselves broad classes of adjuvants, and yet the Examiner asserts that of all of these listed options, one of skill in

the art would select oil-in-water. But Schwartz *et al.* does not teach the necessity of using a costimulatory molecule or even the desirability of such, much less the desirability of oil-in-water over all of the other choices presented. Thus, at best, Schwartz *et al.* only suggests that it would be obvious to try among twenty-nine different costimulatory molecule with an ISS. The Federal Circuit in *In re O'Farrell* stated that:

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or ***try each of numerous possible choices until one possibly arrived at a successful result***, where the prior art gave no indication as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidelines as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Since Schwartz *et al.* fails to provide any teaching that would guide one of skill in the art to select the oil-in-water adjuvant rather than any of the at least twenty eight classes of adjuvants, the two references do not render the claimed invention obvious.

Krieg *et al.* further expands the range of options facing one of skill in the art. Kreig et al. suggest a variety of uses for their CpG oligos including treatment of diseases based on infectious viri that include: Retroviridae (e.g., human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III, LAV or HTLVIII/LAV, or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (e.g., polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g., strains that cause gastroenteritis); Togaviridae (e.g., equine encephalitis viruses, rubella viruses); Flaviridae (e.g., dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (e.g., coronaviruses); Rhabdoviridae (e.g., vesicular stomatitis viruses, rabies viruses); Filoviridae (e.g., ebola viruses); Paramyxoviridae (e.g., parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g., influenza viruses); Bungaviridae (e.g., Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); Arena viridae (hemorrhagic fever viruses); Reoviridae (e.g., reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses);

Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytornegalovirus (CMV), herpes viruses'); Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g., African swine fever virus); and unclassified viruses (e.g., the etiological agents of Spongiform encephalopathies, the agent of delta hepatities (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1 = internally transmitted; class 2 = parenterally transmitted (i.e., Hepatitis Q; Norwalk and related viruses, and astroviruses), infectious bacteria that include: Helicobacterpyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sps (e.g. M. tuberculosis, M. avium, M. intracellulare, M kansaii, M gordonae), Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes (Group A Streptococcus), Streptococcus agalactiae (Group B Streptococcus), Streptococcus (viridans group), Streptococcusfaecalis, Streptococcus bovis, Streptococcus (anaerobic sps.), Streptococcus pneumoniae, pathogenic Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, corynebacterium diphtheriae, corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringers, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponeina pallidium, Treponema pertenue, Leptospira, and Actinomyces israelli; infectious fungi that include: Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Chlamydia trachomatis, Candida albicans; and other infectious organisms (i.e., protists) that include: Plasmodium falciparum and Toxoplasma gondii. Thus, Krieg *et al.* suggest their compositions may be used to treat diseases caused by over one hundred different organisms, without any teaching that would suggest selecting *Neisseria* in particular. Since Krieg *et al.* fails provide any teaching that would guide one of skill in the art to select the *Neisseria*, rather than any of the at least one hundred pathogenic organisms, the two references do not render the claimed invention obvious because 'obvious to try' is not sufficient for obviousness.

B. Agrawal in view of Fraser

Agrawal was cited for teaching compositions comprising a Neisseria antigen and an adjuvant composition comprising a CpG oligonucleotide. Fraser was cited for teaching antigens of

Neisseria meningitidis and *Neisseria gonorrhoeae* including an antigen comprising the amino acid sequence of SEQ ID NO:31 of the instant application, and adjuvants comprising submicron oil-in-water emulsions that can be used in immunogenic compositions. However, Agrawal suggests the use of the CpG oligonucleotide with antigens from a range of organisms including: human immunodeficiency virus (type 1 or 2), influenza virus, herpes simplex virus (type 1 or 2), Epstein-Barr virus, human and murine cytomegalo virus, respiratory syncytial virus, hepatitis B virus, hepatitis C virus, papilloma virus, Plasniodiunifalciparitni, Plasnioditini nialarie, Plasniodiiini ovale, Schistosonta spp., Streptococcus spp., Staphylococcus spp., Pneumococcus spp., Neisseria spp., Vibrio spp., E. coll and Mycobacteritini hibercidosis – a total of 22 organisms of which several are classes that include many organism, notably including *Neisseria*. Fraser suggests a broad range of adjuvants that may be used including: aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; oil-in-water emulsion formulations, muramyl peptides including, but not limited to, N-acetylmuramyl-L-threonyl-D-isoglutarnine (thr-MDP), N-acetyl-normuramyl-L- alanyl-Disoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl- L-alanine-2-(1'-2'dipalmitoyl-sn-glycero-3-huydroxyphosphoryloxy)- ethylamine (MTP-PE), etc., bacterial cell wall components, MF59, SAF, RibiTm adjuvant system (RAS), monophosphorylipid A (MPL), trehalose dimycolate (TDM) , and cell wall skeleton (CWS), preferably MPL + CWS (DetoXTM); saponin adjuvants, such as Stimulon TM, ISCOMs, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA); IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc., interferons (e.g. , gamma interferon), macrophage colony stimulating factor, tumor necrosis factor detoxified mutants of a baeterial ADP- ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an E. coli heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129 – at least 34 different adjuvants which includes classes of adjuvants.

Nothing in either of the two references teaches the desirability of this particular combination of adjuvants and antigens. At best, each teaches that one of skill in the art should try each and every of the at least 34 adjuvants in Fraser with each of the 22 pathogenic organisms that Agrawal suggests for a total of 748 different combinations. Thus, at best, the combined teachings only suggest that it would be 'obvious to try' those 748 different combinations to arrive at the

claimed composition. As discussed above, the Federal Circuit has clearly stated that merely being 'obvious to try' is not sufficient to establish that a claimed invention is obvious.

5. *Summary*

Fraser, et al. does not have a publication date or a 102(e) date that precedes the present application's claim of priority to February 26, 1999. Therefore, unless the Examiner demonstrates that there is a U.S. Application claiming the benefit of Fraser et al. filed before February 26, 1999 or a nation stage filing from Fraser et al. that satisfied the requirements of 35 U.S.C. 371(c)(1), (2), and (4) before February 26, 1999, Applicants respectfully request that the Examiner withdraw the rejection over Agrawal *et al.* in view of Fraser *et al.*

The Examiner has not established a *prima facie* case of obviousness because as discussed above, both rejections fail to teach or suggest "at least 80% of said oil droplets are less than 1 micron in diameter." The Examiner has not established that droplet size and ratios are result effective variables, which is required for optimization to be obvious. See, e.g., *In re Antonie*, 559 F.2d 618 (CCPA 1977).

In addition, as discussed above, the Examiner has not demonstrated that one of skill in the art would be motivated to combine either pair of references. A motivation to combine references is necessary in order to establish a *prima facie* case of obviousness when more than one reference is used in the rejection.

Finally, give that both rejections include a broad disclosure of a wide range of choices of organism and adjuvants to combine without any guidance to select the particular claimed combination, even if there was motivation to combine the respective pairs of references and all elements were taught or suggested, it would still only result in the claimed invention being 'obvious to try' among an array of possible combinations, which is not sufficient for a § 103 rejection.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

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CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **223002102200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: July 10, 2006

Respectfully submitted,

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